Remarks/Arguments

No claim amendment is made in this submission. Claims 18-19 and 23-24 are pending and under consideration.

The Examiner has rejected the pending claims under 35 U.S.C. 103(a) as being unpatentable over Reid (N. Engl. J. Med., 2002) and Coleman (Breast Cancer, 2000). The Examiner argues it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the methods of Reid in treating bone loss in patients suffering from bone loss that arises as a result of receiving letrozole. Applicants respectfully disagree.

The present invention defines methods of treating bone loss in a patient comprising administering zoledronic acid or a pharmaceutically acceptable salt thereof, wherein the patient is either suffering from an estrogen dependent disorder and receiving letrozole or wherein the patient is a postmeopausal woman with Er+ and/or PR+ breast cancer and receiving letrozole. The present invention also defines methods of treating bone loss comprising administering to a patient in needs of such treatment and effective amount of zoledronic acid wherein the bone loss is caused by the treatment with letrozole. Support for the claims can be found throughout the specification and Examples. Example 6, starting on page 50 of the specification describes the effectiveness of intravenous administration of zoledronic acid in preventing the bone loss and reduction of mechanical properties induced by aromatase inhibition or surgical ovariectomy in rats. The results showed a single iv injection of 0.8 μg/kg zoledronic acid delayed bone loss significantly for 24 weeks in patients treated with letrozole with the highest dose being full protective over the entire 24-week duration of the study, page 51 lines 6-10 of the specification. The findings of this study were summarized on page 52 of the specification:

> Discussion: Our data indicates for the first time that in rats, Zol dose-dependently protects against cancellous bone loss, corical thinning and reduction of bone strength induced by daily oral letrazole, at a dose of 20μg/kg, fully protects against letrozole induced bone loss for at least 24 weeks.

None of the references alone or in combination describe the methods of treatment of the present invention. Reid et al. discussed the effects of five zoledronic acid regimens on bone turnover and density in 351 postmenopausal women with low one mineral density in a one year, randomized, double-blind, placebo-controlled trial. The results of the trial were that zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures. The results suggested that an annual infusion of zoledronic acid might be as an effective treatment for postmenopausal osteoporosis. Reid does not teach or suggest

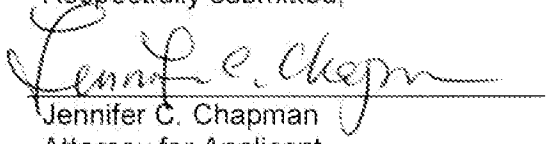
the use of zoledronic acid for the treatment of cancer patients suffering from bone loss associated with treatment from the cancer drug letrozole.

Despite Examiner's acknowledgment that "Reid does not teach that the patients administer zoledronic acid are suffering from bone loss resulting from bone loss resulting from the administation of letrozole," the Examiner asserted that "one of ordinary skill in the art would find it obvious to treat the bone loss regardless of the cause of the bone loss". Applicants respectfully submit that such assertion is not proper. As stated in our previous Response, it has been acknowledge by the United States Court of Appeals for the Federal Circuit that the nature of bisphosphonates are unpredictable, *Procter & Gamble Co. vs. Teva Pharma (Fed. Cir. 2009)*. Applicants disagree with the Examiner's statement that one of ordinary skill in the art would find it obvious to treat bone loss associated with letrozole based on the teachings of Reid. Reid discloses a patient population unaffected by cancer. The patients associated with the clinical trial were healthy post-menopausal women with low bone mineral density. The outcome of that trial suggested that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis. The "patient" of the present invention had taken or is currently taking letrozole for the treatment of cancer. The side-effects of taking letrozole is bone loss. Reid does not teach or suggest utilizing the annual infusion of zoledronic acid to treat patients suffering from bone loss associated with taking another cancer therapy.

Applicants respectfully submit that, as evidenced by various publications available at the time the instant application was filed, success was not anticipated for employing the administration of an aromatase inhibitor and a bisphosphonate. Coleman describes the use of zoledronic acid but it does not teach or suggest using zoledronic acid for the treatment of bone loss in patients taking letrozole. None of the cited references described the unexpected results found by combining letrozole with zoledronic acid.

Applicants respectfully request the obviousness rejection be withdrawn from consideration.

Respectfully submitted,



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